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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/595,821	01/16/2007	August Verbruggen	50304/021002	7212

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EXAMINER	
ARIANI, KADE	
ART UNIT	PAPER NUMBER
1651	

NOTIFICATION DATE	DELIVERY MODE
06/03/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/595,821	VERBRUGGEN ET AL.	
	Examiner	Art Unit	
	KADE ARIANI	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/16/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The preliminary amendment filed on 05/12/2006, 2005, has been received and entered.

Claims 1-22 have been canceled.

New Claims 23-42 have been added.

Claims 23-42 are pending in this application and were examined on their merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 27 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 27 recites the limitation " unsulphated alginate". There is insufficient antecedent basis for this limitation in the claim. Because there is no "unsulphated alginate" claim 23.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 23-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kavalkovich et al. (In vitro Cell. Dev. Biol. - Animal, 2002, Vol. 38, p.457-466) in view of Ronghua et al. (Carbohydrate Polymers, April 2003, Vol. 52, p.19-24) and further in view of Kawada et al. (Arch Dermatol Res, 1999, Vol. 291, p.542-547) and further in view of Rihova B. (Advanced Drug Delivery Reviews, 1996, Vol. 21, p.157-176).

Claims 23-30 are drawn to an *in vitro* method for the cultivation of connective tissue cells, comprising the step of contacting said cells with a matrix comprising polysulphated alginate, the matrix is further comprises nutrient media, the matrix is further comprises unsulphated alginate, polysulphated alginate and alginate are present in a weight ration of between 1:10 and 1:100, said cells are connective tissue cells, cells are chondrogenic cells, and cells are chondrocyte precursor cells.

Claims 31-38 are to a matrix comprising polysulphated alginate and mammalian connective tissue cells, cells are osteochondral cells, chondrogenic cells, mesenchymal stem cells, the matrix further comprises nutrient medium, said polysulphated alginate is present in a concentration between 100 ng and 500 µg/ml, the matrix further comprises unsulphated alginate, and a pharmaceutical composition comprising a matrix according to claim 31.

Claims 39- 42 are drawn to a method for the treatment of osteochondral defects comprising administering to the osteochondral defect a matrix comprising a polysulphated alginate, said matrix further comprises connective tissue cells, cells are osteochondral cells, and cells are chondrogenic cells.

Kavalkovich et al. teach to an *in vitro* method for the cultivation of connective tissue cells, comprising the step of contacting mesenchymal stem cells with a matrix (three-dimensional format) comprising unsulphated alginate (2.4% sodium alginate), the matrix is further comprises nutrient media (chondrogenic media) (Abstract, p.457 2nd column end paragraph lines 1-4, p.458 2nd column 1st paragraph line1 and 2nd paragraph Lines 2-3 and 14-15). Kavalkovich et al. teach mesenchymal stem cells have the capacity to differentiate in to chondrocytes (chondrogenic potential), which has been demonstrated *in vivo* by implantation (p.457 1st column 1st paragraph lines 1-5). Kavalkovich et al. teach the studies have led to the definition of conditions where chondrogenesis optimally occurs, and the enhancement of mesenchymal stem cells chondrogenesis described in this in vitro system, would provide insights into conditions and events influencing chondrogenesis and on regenerative tissue strategies (p.458 1st column 2nd paragraph lines 4-12).

Kavalkovich et al. teach because cartilage has poor regenerative capacity, cell therapy is a attractive option either for retarding degenerative changes in the case of osteoarthritis of for restoring functional tissue after traumatic injury (a method for the treatment of osteochondral defect) (p.464 1st column end paragraph lines 1-4).

Kavalkovich et al. do not teach polysulphated alginate, and polysulphated alginate and unsulphated alginate are present in a weight ration of between 1:10 and 1:100. However, Ronghua et al. teach alginate sulfates (AS) has anticoagulant activity (Abstract and Introduction 2nd column end paragraph lines 1-6, and p.20 Scheme 1.). Ronghua et al. teach alginate sulfates showed anticoagulant activity (APTT) in a dose dependent manner, as 226 s at about 17 µg/ml (p.23 1st column 2nd paragraph line 6-7, and Figure 3.). It must be noted that a person of ordinary skill in the art at the time the invention was made would have realized that thrombogenicity is one of the discriminating factor between compatible and non-compatible materials, and a matrix suitable for implantation, must be non-thrombogenic to be biocompatible (see Rihova, p.163 1st column 2.3.2. 7-10). Ronghua et al. further teach for some applications the anticoagulant activity must be decreased (p.20 1st column 2nd paragraph lines 1-2).

Further motivation to use unsulphated alginate is in Kawada et al. who teach unsulphated alginate (alginate with no sulfate group) at the concentration 1 µg/ml stimulated endothelial cell migration and proliferation (Abstract and p.546 1st column 2nd paragraph lines 17-19, and 3rd paragraph lines 8-14). It must be noted that a person of ordinary skill in the art at the time the invention was made would have realized that stimulation of endothelial cell migration and proliferation were necessary for vascularization of the implant.

Therefore, a person of ordinary skill in the art at the time the invention was made knowing that a biocompatible matrix (suitable for implantation) must be non-thrombogenic, would have been motivated to modify the method as taught by

Kavalkovich et al. according to the teachings of Ronghua et al. and to use polysulphated alginate to provide an in vitro method for the cultivation of connective tissue cells and a pharmaceutical composition comprising the matrix, and a method for the treatment of osteochondral defect, with a reasonable expectation of success, because Ronghua et al. teach alginate sulfates (AS) has anticoagulant activity.

Accordingly, a person of ordinary skill in the art at the time the invention was made knowing that Ronghua et al. teach alginate sulfates showed anticoagulant activity at about 17 µg/ml, would have been motivated to optimize the concentrations and weight ratio of the polysulphated alginate to alginate to be added to the matrix in the method of Kavalkovich et al. by routine experimentation.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kade Ariani whose telephone number is (571) 272-6083. The examiner can normally be reached on 9:00 am to 5:30 pm EST Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kade Ariani
Examiner
Art Unit 1651

/Leon B Lankford/
Primary Examiner, Art Unit 1651